Radiotherapy-Induced Lung Cancer among Women Who Smoke

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It comes as no surprise that radiation at high doses can cause lung cancer. Survivors of the atomic bomb explosions in Japan,[1,2] patients given radiotherapy for ankylosing spondylitis[3] or lymphoma,[4–7] and underground miners exposed to radon[8] all have been reported to be at increased risk of lung cancer. There is growing evidence that adjuvant radiotherapy for breast cancer after radical mastectomy, a common treatment practice in previous decades, but less so today, also is associated with an increased risk of lung cancer 10 or more years later.[9,10] For medically exposed populations, it is important to understand the magnitude of possible treatment risks, the associated benefits, and the relevance to current practice. The joint effects of radiation and other environmental exposures, most notably cigarette smoking, also await clarification and are of scientific interest for what they may imply about the mechanisms of lung carcinogenesis.[11]

The paper by Neugut and colleagues in this issue[12] addresses the combined effects of radiation therapy and smoking, with a view toward the possible clinical implications. The authors report a 3-fold relative risk (RR) associated with radiotherapy for breast cancer among 10-year survivors, a 14-fold RR associated with cigarette smoking, and a 33-fold risk among irradiated smokers. Each of these associations was more pronounced for lung cancers occurring in the lung on the same side of the body as the breast cancer (ipsilateral) than for those occurring on the opposite (contralateral) and less heavily irradiated side. The authors suggest that radiotherapy and smoking act multiplicatively and that smokers represent a subgroup in which the absolute risks associated with radiotherapy are much greater than for nonsmokers, large enough, perhaps, to be an important consideration in the design of breast cancer treatment for smokers.

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The authors acknowledge the limitations of their study and the differences between past and current radiotherapy techniques, which together limit the generalizability of the findings. Limitations include the small size and reliance on registry data to classify women by radiotherapy and smoking status. Information about smoking history was missing altogether, and even current smoking, as of the time of the second malignancy, was unknown for a large percentage of cases (22%) and a still larger percentage of controls (43%). The higher RR associated with smoking for ipsilateral lung cancer than for contralateral lung cancer among nonirradiated women, although possibly a chance finding, also might signal an unidentified bias. Information about radiotherapy at the level of “yes” or “no” generally was available, but even if these data were accurate, dose to the lungs for individual women was not known.

Women with second primary breast cancers accounted for 65% of the control series. Breast tissue in young women is highly sensitive to the carcinogenic effects of ionizing radiation.[13] However, this sensitivity declines with age and, as Neugut et al. point out, available evidence indicates that radiotherapy is responsible for few (< 3%) second primary breast cancers occurring among breast cancer patients.[14,15] Furthermore, such an effect, if present, would tend to bias estimates of the RR of lung cancer associated with radiation therapy toward 1.0. Concern about the control series centers more on the comparability of the quality of information on smoking with that for the cases than on possible causal associations with cigarette smoking or radiotherapy. Smoking habits clearly were ascertained more frequently among patients with lung cancer, and the possibility of bias in ascertainment moderates conclusions that might be drawn.

Although the observed relationship between radiotherapy and smoking was described as multiplicative, it may be characterized more accurately as submultiplicative, consistent with a multiplicative relationship but also, perhaps, with additivity. The “expected” results assuming additivity of risks versus multiplicative risks can be evaluated using the data from Table 3 of Neugut et al. and temporarily ignoring sampling error and possi-

Table 1. Excess Relative Risks for Breast Cancer, Based on Data From Neugut et al.

	Radiation therapy	
Smoking	*No*	*Yes*
No	0	2.2x
Yes	13.5x	31.7x

ble bias in the ascertainment of smoking. Data are reexpressed in Table 1, in terms of the excess relative risk (RR- 1). By definition, there is zero excess risk for the reference group of nonirradiated nonsmokers (1 – 1 = 0). The excess risk in each of the other three cells is expressed as a multiple of the incidence rate for the reference category. If excess relative risks were additive, irradiated smokers would be expected to have an excess relative risk of 13.5x + 2.2x = 15.7x and an overall relative risk of 16.7 (=15.7 + 1). Assuming that the two exposures act multiplicatively, and given the RR (odds ratios) reported in Table 3 of Neugut et al. for radiation therapy (RR = 3.2) and smoking (RR = 14.5) individually, irradiated smokers would be expected to have a RR of 46.4 (= 3.2 x 14.5). The observed RR of 32.7 is intermediate between these two values. Of course, there is a sampling error in the RR for radiotherapy and smoking individually as well as for combined exposure. No formal tests of goodness of fit for additive or multiplicative models were presented, but data would appear to be statistically compatible with either.

Other populations for which the combined effects of irradiation and smoking have been studied include uranium miners and survivors of the atomic bomb explosions in Japan. Recent analyses of data for miners tend to support either a submultiplicative or multiplicative relationship; models based on the additivity of excess relative risks fit poorly.[8] For atomic bomb survivors, multiplicative and additive models seemed to fit equally well.[8] It is important to consider differences between these populations. The miners, predominantly men, were exposed chronically over a working lifetime to densely ionizing (high linear energy transfer) alpha radiation from inhaled radon daughter products. Atomic bomb survivors were exposed nearly instantaneously, mostly to sparsely ionizing (low linear energy transfer) gamma radiation and, to a lesser degree, to neutrons. Dose distribution within the lung likely would have been more uniform than for the miners. Adjuvant radiotherapy of breast cancer in Connecticut typically was done with cobalt-60 gamma rays or orthovoltage radiographs, whereas megavoltage treatments are used more often today.[12,14] Exposures were fractionated and delivered over a period of weeks. Local doses to parts of the lung in the radiation field would have been much higher than for the atomic bomb survivors. Radiation type and energy, dose and dose rate, and volume of lung irradiated differed among the three study populations, and the differences may be important in determining the joint effects of irradiation and smoking.

The finding of a positive association between lung cancer risk and breast cancer radiotherapy for ipsilateral, but not contralateral, lung cancer is proposed by Neugut et al. as further evidence of a radiogenic effect, because lung doses would have been higher on the ipsilateral side. However, doses would not have been negligible on the contralateral side. The experimental values for dose to the ipsilateral and contralateral lungs for cobalt treatments (Table 4, Neugut et al,) differed by a factor of less than 2. A recently completed study (Inskip, et al., unpublished data) that included radiation dosimetry for individual breast cancer patients confirmed that dose to the contralateral lung was high, of the order of a few gray. It is peculiar that a zero or low risk associated with radiotherapy was seen for the contralateral lung. To be sure, the confidence interval around this RR was very wide, and even high RR cannot be ruled out. If, however, the low observed risk for cancer of the contralateral lung is interpreted as indicating the absence of a radiation effect, then one would also have to infer that risks associated with more modern treatments (conservative surgery with breast irradiation) probably are substantially lower than those attributable to adjuvant radiotherapy after mastectomy, perhaps by several-fold. The applicability of these results to contemporary clinical practice is questionable, but possibly reassuring.

Risks need to be balanced against the therapeutic benefits of radiation in combating a life-threatening disease. Neugut et al. reported no evidence of excess risk associated with radiotherapy for intervals less than 10 years after treatment. Interestingly, in their previous paper based on Surveillance, Epidemiology, and End Results registry data, Neugut et al.[10] reported a deficit of lung cancer among irradiated women during the first 10 years after treatment for breast cancer, an excess in later years, and no association with radiation therapy overall. In the current series, data for intervals greater than or equal to 10 years posttreatrnent are grouped together, so it is not clear whether or how the RR varied with increasing time. If the overall RR associated with radiotherapy (3.2) represents an average of an RR that was increasing over time, then it is possible that the excess risk was concentrated among the long-term survivors, that is, those who survived for at least 15–20 years after treatment, Such patients can be said to have had favorable treatment outcomes, at least with respect to survival, whether or not the radiation therapy was responsible.

Issues in need of clarification concerning the joint effects of smoking and radiotherapy include the importance of simultaneity or sequencing of exposures and the effect of quitting smoking.[8] Temporality of combined exposure to radiation and cigarette smoke appears to influence the level of risk.[11,16] The quantitative aspects of radiation therapy and smoking also need to be addressed. This is particularly important in light of reductions in lung dose associated with current radiotherapy practices. Long-term follow-up of women treated by breast-conserving surgery and irradiation is necessary to evaluate these risks. Other studies suggest that thoracic radiotherapy for other cancers, including Hodgkin's disease, may also be associated with an increased risk of lung cancer,[5–7] and pooling of data from different study populations may provide opportunities for new insights. Future investigations also should address the possible risks of lung cancer associated with chemotherapy and the joint effects of chemotherapy and radiation therapy. Where sample sizes permit, analyses should be done separately for the major histologic types of lung cancer.

Regardless of whether the combined effects of radiotherapy and cigarette smoking are multiplicative or submultiplicative, the following observations would appear to hold. First, the absolute risks of lung cancer associated with current breast cancer radiotherapy practices probably are small. Based on data from Harvey and Brinton[9] for 10-year survivors of breast cancer in Connecticut, adjuvant radiotherapy as practiced in past decades might be expected to cause an extra seven to eight cases of lung cancer per year among 10,000 irradiated women who survive 10 years. Risks from localized radiotherapy almost certainly are lower, regardless of smoking status, and much less than the risk of death due to metastatic breast cancer. The incidence rate for all second primary cancers combined among nonirradiated 10-year survivors of breast cancer was 165 per 10,000 person-years.[9] Continued research will clarify the efficacy, costs, and benefits of different breast cancer treatment plans, including conservative surgery with breast irradiation. It would not seem prudent at this time to modify, and possibly compromise, breast cancer treatment plans of demonstrated value on the basis of concerns about possible late cancer effects of radiotherapy regardless of the smoking status of the patient. On the other hand, we do not require further study to advise a breast cancer patient who smokes on how she might lower, or more accurately, slow the rate of increase of her risk of lung cancer. She can do so by quitting smoking. Health benefits of quitting smoking are apparent even before 10 years have passed.

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